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Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence and epidemiology

Endometrial cancer is now the most common gynaecological malignancy in Europe and North America. It is the seventh most common cause of death from cancer in women in Western Europe, accounting for 1%–2% of all deaths from cancer. About 81 500 women are affected every year in the European Union and the incidence is increasing. Median age of occurrence is 63 years, while >90% of women are older than 50.

Roughly 75% of women survive for 5 years as most women are being diagnosed at an early stage because of irregular vaginal bleeding. At diagnosis, ∼75% of women have disease confined to the uterus (stage I). Five-year survival for stage I patients is 90%. In some cases, a history of complex hyperplasia/atypia can be demonstrated. The majority of endometrial cancers occur after menopause, but up to 25% of cases may be premenopausal.

Risk factors for developing endometrial cancer are: obesity, nulliparity, late menopause, diabetes melitus and prolonged, unopposed estrogen exposure, tamoxifen and the oral contraceptive pill.

endometrial cancer histological types

The most common type is endometrioid adenocarcinoma, which is composed of malignant glandular epithelial elements. Clear-cell and papillary serous carcinoma of the endometrium are tumours that are histologically similar to those noted in the ovary and the Fallopian tube, and the prognosis is worse relative to adenocarcinomas.

1. Endometrioid (75%) (secretory, ciliated, papillary or villoglandular)
2. Adenocarcinoma with squamous differentiation.
3. Adenoacanthoma (benign squamous component)
4. Adenosquamous (malignant squamous component)
5. Uterine papillary serous (5%–10%)
6. Clear cell (1%–5%)
7. Malignant mixed Mullerian tumours or carcinosarcomas (1–2%)
8. Uterine sarcomas (leiomyosarcoma, endometrial stromal sarcoma, undifferentiated) (3%)
9. Mucinous (1%)
10. Undifferentiated.

Based on histopathology, molecular profile and clinical course of endometrial cancers are divided into two categories. Type I are typically low-grade (I–II) adenocarcinomas that are usually estrogen related, are diagnosed early and have a favourable prognosis.

Type II endometrial cancers are not hormone dependent and are usually grade III endometrioid adenocarcinomas, papillary serous and clear cell carcinomas and carcinosarcomas (malignant mixed Mullerian tumours). They have p53 mutations and loss of heterozygosity at several chromosomal loci. They are associated with early spread and worse prognosis. It is interesting that some type II tumours may have molecular alterations found in type I tumours such as K-ras, PTEN, β-catenine and microsatellite instability. This indicates that type II tumours can arise from dedifferentiation of a pre-existing type I cancer.

staging

The FIGO (International Federation of Gynecology and Obstetrics) staging system for endometrial cancer has been revised recently. The previous staging is shown in Table 1 and we have included it in this guideline, as the existing literature and evidence are based on this. The new staging is shown in Table 2, and hopefully it will be used in the next guidelines.

The initial preoperative evaluation apart from history and clinical examination and endometrial biopsy, includes complete blood count, liver and renal function tests, and chest X-ray. If cervical involvement is suspected, contrast-enhanced dynamic magnetic resonance imaging (MRI) should be requested.

FIGO uses surgical and pathological staging for carcinoma of the uterus (Tables 1 and 2). Pathological assessment includes:

- depth of myometrial invasion (ratio of invasion to total myometrial thickness);

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Table 1. The 'old' FIGO staging for endometrial cancer: it is included here as the currently existing literature is based on this and t would be useful for the reader to take it into account when reading the present guidelines

Stage	
IA	Tumour limited to endometrium
IB	Invasion to <50% of the myometrium
IC	Invasion to >50% of the myometrium
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
IIIA	Tumour invades serosa and/or adnexa and/or positive peritoneal cytology
IIIB	Vaginal metastases
IIIC	Metastases of pelvic and/or para-aortic lymph nodes
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes

Table 2. The new 2009-FIGO staging for endometrial cancer

Stage	
I	Tumour confined to the corpus uteri
IA	No or <50% of the myometrium
IB	Invasion ≥50% of the myometrium.
II	Tumour invades cervical stroma but does not extend beyond the uterus
III	Local and/or regional spread of the tumour
IIIA	Tumour invades serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC1	Positive pelvic lymph nodes
IIIC2	Positive para-ortic lymph nodes with or without pelvic nodes
IV	Tumour invades bladder/bowel mucosa, and/or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes

- cervical involvement (glandular/stromal invasion);
- tumour size and location (fundus, lower uterine segment/cervix);
- extension of tumour to Fallopian tubes and ovaries;
- tumour grade and histological cell subtype (adenocarcinoma versus clear cell, papillary serous);
- lymphovascular space invasion (LVSI);
- lymph node status. The approximate incidence of pelvic lymph node involvement is for FIGO stage IA: 5%, IB: 10%, IC: 15%, II: 20%, III: 55%.

treatment

surgery

Most patients (75%) with endometrial cancer are diagnosed with stage I disease, as a result of an early investigation of abnormal postmenopausal bleeding.

Patients are treated initially by total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) [I, A]. Operation may be either an open or a laparoscopic procedure. A pelvic/para-aortic lymphadenectomy may be carried out, although the practice varies between centres. Debate about the role of lymphadenectomy is ongoing as it may increase the risk of lymphoedema without a clear benefit. A randomized trial of lymphadenectomy and adjuvant external beam radiotherapy in the treatment of endometrial cancer conducted by the Medical Research Council (MRC) and the National Cancer Research Institute (NCRI) in the UK. There was no evidence of benefit on overall survival or recurrence-free survival for pelvic lymphadenectomy in women with early endometrial cancer and it cannot be recommended as routine procedure for therapeutic purposes. However, complete surgical staging is suggested by others that may have an impact on survival.

Abdominal organs such as the liver, diaphragm, omentum, peritoneal surfaces are inspected and palpated during operation. Peritoneal washings are also taken. Patients with suspected cervical involvement (after an MRI or cervical biopsy) would preferably be treated by radical total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) and pelvic/para-aortic lymph node dissection is considered.

Medically inoperable stage I/II patients (with comorbidities common to those patients, obesity, cardiac morbidity, diabetes) may be treated by external beam radiotherapy (RT) and/or brachytherapy (BT) [I, A].

In patients with intra-abdominal disease (omental, nodal, ovarian, peritoneal involvement, ascites) TAH/BSO and maximal surgical debulking could be considered. In patients with distant metastatic disease (e.g. liver, lung) palliative hysterectomy could be considered depending on patient status, expected benefits and multidisciplinary team decision. Surgery may be followed by pelvic RT and/or chemotherapy (see below).

adjuvant postoperative treatment

There is no definitive data supporting the routine use of adjuvant treatment for patients with disease confined to the uterus. There is uncertainty as to whether adjuvant RT improves overall survival. Factors influencing the decision for adjuvant treatment are mentioned above in the paragraph on staging.

Data from randomized studies such as PORTEC-1 (Postoperative Radiation Therapy in Endometrial Carcinoma), the GOG-99 (Gynecologic Oncology Group) and the recent ASTEC/EN.5 trial have shown a reduction in locoregional disease recurrence but not benefit in overall survival. Similar findings were reported by others. Those studies have shown that the majority of the initial recurrences for patients with disease limited to the uterus were limited to the vagina, suggesting that vaginal vault brachytherapy alone could be used as an adjuvant treatment. To compare adjuvant pelvic RT with vaginal BT alone in uterine-confined disease, the PORTEC-2 study randomized patients between those two modalities and showed very satisfactory vaginal and pelvic control rates and equal survival with both modalities.

role of chemotherapy

adjuvant chemotherapy

Despite a traditional use of adjuvant radiotherapy, stage I/II patients with high-risk factors may have a compromised survival due to extrapelvic metastatic disease, suggesting the need for an effective systemic adjuvant therapy. The EORTC 55991 randomized trial is a study of adjuvant RT with or without chemotherapy in high-risk patients stage I/II tumours with deep myometrial invasion and grade 3, clear cell, serous papillary, undifferentiated pathology. Initially chemotherapy consisted of four courses of cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2 or epirubicin 75 mg/m^2 (AP). Subsequently several chemotherapy regimens were allowed, of which AP, paclitaxel 175 mg/m^2 + epirubicin 60 mg/m^2 + carboplatin AUC 5, and paclitaxel 175 mg/m^2 + carboplatin AUC 5–6 were used. Data from this trial showed that adjuvant chemotherapy given before or after RT results in a hazard ratio (HR) for progression-free survival of 0.58 in favour of RT + chemotherapy [95% confidence interval (CI) 0.34–0.99; $P = 0.046$]. This translates to an estimated 7% absolute difference in 5-year progression-free survival from 75% (95% CI 67%–82%) to 82% (95% CI 73%–88%).

Two large randomized studies from Italy and Japan have failed to show any difference in overall survival or progression-free survival between chemotherapy and RT and there is an ongoing debate on the methodology and the results of those trials.

To resolve this issue an intergroup trial of the Dutch Cooperative Gynaecologic Oncology Group and the UK NCRI has conducted the PORTEC 3 study, a randomized trial comparing concurrent chemoradiation and adjuvant chemotherapy with pelvic radiation alone in high-risk and advanced-stage endometrial carcinoma (stage IB grade 3 with LVSI; stage IC or IIA grade 3; stage IIB; stage III; stage IB, IC, II or III with serous or clear cell pathology).

chemotherapy for advanced or recurrent disease

Two large randomized studies (EORTC 55872 and GOG-107) have compared doxorubicin and cisplatin (AP) with doxorubicin, and found that the combination gave better response rates, but no significant differences in survival. Mainly on the superior response rates, the combination of doxorubicin and cisplatin has been used as a standard treatment in endometrial cancer. Other combinations with or without taxanes are being studied.

A recent Cohrane Review included trials accruing women with advanced/recurrent/metastatic endometrial adenocarcinoma (not amenable to potentially curative surgery or radical RT) who were suitable for cytotoxic chemotherapy. Meta-analysis has shown that progression-free survival was significantly improved (HR = 0.80; 95% CI 0.71–0.90; $P = 0.004$), but there was only a trend towards improved survival (HR = 0.90; 95% CI 0.80–1.03). Addition of paclitaxel to combination chemotherapy was at the expense of increased toxicity [I, A]. Other randomized trials are currently ongoing (e.g. GOG-209).

A study with an impact on the treatment of endometrial cancer with chemotherapy was GOG-122. Four hundred patients with FIGO stage III or IV endometrial carcinoma of any histology (including serous and clear cell carcinomas) were randomized. The study compared chemotherapy with whole abdominal RT of 30 Gy in 20 fractions with an additional 15 Gy pelvic boost. Eligibility required TAH and BSO, surgical staging, tumour resection and no single site of residual tumour greater than 2 cm. Nodal sampling was optional. Chemotherapy consisted of doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) every 3 weeks for seven cycles, followed by one cycle of cisplatin. Both overall survival and progression-free survival were significantly better for patients treated in the chemotherapy arm.

hormone therapy

Hormone therapy as an adjuvant treatment is not recommended. For advanced or recurrent disease, oral medroxyprogesterone acetate had an overall response rate of 25% and 200 mg/day works equally well as 1000 mg/day. Patients with well-differentiated tumours and positive progesterone receptor status have a higher response rate. Tamoxifen (40 mg/day) combined with medroxyprogesterone acetate (200 mg/day) may have a higher response rate.

papillary serous, clear cell carcinomas

Papillary serous and clear cell carcinomas are considered more aggressive (type II endometrial cancers) and have a higher incidence of metastatic disease (and patterns of failure with a similarity to ovarian cancer), and lower 5-year survival rates than patients with endometrioid carcinoma. The EORTC 55991 and the PORTEC 3 trials have included patients with these histologies, so it is expected that the role of adjuvant chemotherapy and RT in these patients will be answered by these studies.

recurrent disease

Disease usually recurs within the first 3 years following initial treatment. After the diagnosis of the recurrence a full staging with complete blood tests and imaging for assessment of the disease extent is important for discussion of therapeutic options. Surgery is considered only in solitary/isolated recurrences (e.g. single lung metastasis), and in cases where it is hoped it will improve the patient's symptoms and quality of life. Pelvic exenteration can be considered in fit patients with an isolated central recurrence.

However, RT is the most commonly used treatment modality for pelvic recurrence of endometrial carcinomas. In fit patients without extrapelvic disease, pelvic RT followed by vaginal BT may offer a 5-year survival rate of 30%–80%. Pelvic recurrences are most commonly found at the vaginal vault. If the remaining tumour after pelvic RT is <3–5 mm, intracavitary BT can be used. Otherwise, interstitial BT can be considered if available. Chemotherapy can also be considered especially in the case of disseminated extrapelvic disease. Options need to be examined in the multidisciplinary meeting and discussed with the patient. Decisions should be taken after balancing the expected benefits and side-effects from cytotoxic chemotherapy. The most active

agents against recurrent endometrial cancer are doxorubicin and *cis*-platinum.

Hormonal therapy may give response rates as high as 20%–30% (see above).

guidelines for adjuvant treatment for endometrial cancer could be as follows

Treatment guidelines for endometrial cancer cannot incorporate all possible options and individual patients' cases. Controversy and lack of clear evidence characterize this heterogeneous neoplasmatic disease. It is therefore recommended that the decision for treatment of endometrial cancer should be based on discussion in a multidisciplinary team with participation of all the involved diagnostic and therapeutic specialties.

(Staging is referred to according to the 'old' staging as trials and evidence are based on this staging—Table 1.)

stage IA G1–2, IB G1–2. Observation.

stage IA G3, IB G3. Patients with stage IA G3 and IB G3 could be considered for vaginal BT, depending on coexisting risk factors (see above). In the case of LVSI and positive or no lymph nodes dissected in a patient with a stage IB G3 tumour, pelvic RT can be considered.

stage IC, G1–2. Observation or vaginal BT. Pelvic RT as above in stage IB G3.

stage IC, G3. Vaginal BT alone or pelvic RT in case of LVSI, positive nodes or no nodes dissection can be considered. Chemotherapy should be discussed for those high-grade patients.

stage II. Patients with **stage IIA** (cervical glandular involvement only) without other risk factors are being treated as those with stage I. It has to be mentioned that in the 'new' FIGO staging system the involvement of cervical glands is not staged as a stage II disease. Involvement of cervical stroma had been staged as a **stage IIB** high-risk tumour, where both pelvic RT and vaginal BT should be considered. In the case of grade I tumour without LVSI and/or negative pelvic nodes after node dissection, vaginal BT alone could be considered.

It has also been suggested that adjuvant chemotherapy may reduce the rate of distant recurrences in these patients. Therefore, it is reasonable to consider adjuvant chemotherapy for high-grade (grade 3) tumours with cervical stromal invasion.

stage III and IV. Treatment for patients with stage III–IV disease should be individualized to the needs, prognosis and clinical condition of each patient. A multimodality approach is indicated, tailored to the extent of the disease and the histological subtype. Maximal surgical cytoreduction is considered if feasible, for patients without co-morbidities [III, B]. Tumours that are outside the uterus but not outside the pelvis (stage III) are approached with curative intent.

Observation only could be an option for non-invasive grade I–II, confined to fundus tumours with only positive cytology (stage IIIA with the old staging). For **all other stage III** tumours pelvic RT with vaginal BT (especially in case of cervical stroma invasion) is recommended.

Adjuvant chemotherapy may reduce the rate of distant recurrence in these patients. Therefore, it is reasonable to consider adjuvant chemotherapy for stage III high-grade tumours, particularly those with pelvic lymph node disease, in addition to adjuvant RT.

Neoadjuvant chemotherapy can be considered for tumours advanced at diagnosis. This may be followed by surgery. Pelvic RT could be considered either to palliate symptoms or as a high-dose palliative RT if it was felt it could offer a longer free-of-symptoms interval.

papillary serous and clear cell carcinomas

No definite evidence could support therapeutic options (see above) for patients with papillary serous, clear cell carcinoma. However, for the purpose of this guideline adjuvant therapy recommendations could be [III, B]:

stage IA. Observation or chemotherapy or pelvic RT.

stage IB–II. Chemotherapy with or without pelvic RT, with or without vaginal BT (especially in cervical stromal invasion).

stage III–IV. Adequately debulked: chemotherapy and pelvic RT with or without vaginal BT (especially if there is cervical stromal invasion). Chemotherapy is considered in inadequately debulked stage III or IV patients.

follow-up

Patients treated for endometrial cancer should be followed up for both recurrence and late toxicity. Although there is lack of evidence for clear benefit and follow-up schedules vary between centres, the following schedule could be advised. For the first 3 years patients can be seen 3- to 4-monthly. History, physical and vaginal examination should be performed. Further investigations (CT, MRI, blood tests, examination under anaesthesia) can be requested if clinically indicated. For the next 2 years and until the completion of 5 years in total, 6-monthly appointments are recommended. During this surveillance the increased risk of cancers of the breast, ovary and colon in patients with endometrial cancer should be taken into account.

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